Pharmacokinetics of *Naja sumatrana* (Equatorial Spitting Cobra) Venom and Its Major Toxins in Experimentally Envenomed Rabbits

Michelle Khai Khun Yap¹, Nget Hong Tan¹, Si Mui Sim², Shin Yee Fung¹, Choo Hock Tan²

¹Centre and Department of Molecular Medicine, Faculty of Medicine, University of Malaysia, Kuala Lumpur, Malaysia; ²Department of Pharmacology, Faculty of Medicine, University of Malaysia, Kuala Lumpur, Malaysia

Abstract

**Background:** The optimization of snakebite management and the use of antivenom depend greatly on the knowledge of the venom's composition as well as its pharmacokinetics. To date, however, pharmacokinetic reports on cobra venoms and their toxins are still relatively limited. In the present study, we investigated the pharmacokinetics of *Naja sumatrana* (Equatorial splitting cobra) venom and its major toxins (phospholipase A₂ neurotoxin and cardiotoxin), following intravenous and intramuscular administration into rabbits.

**Principal findings:** The serum antigen concentration-time profile of the *N. sumatrana* venom and its major toxins injected intravenously fitted a two-compartment model of pharmacokinetics. The systemic clearance (91.3 ml/h), terminal phase half-life (13.6 h) and systemic bioavailability (41.9%) of *N. sumatrana* venom injected intramuscularly were similar to those of *N. naja* venom determined in an earlier study. The venom neurotoxin and cardiotoxin reached their peak concentrations within 30 min following intramuscular injection, relatively faster than the phospholipase A₂ and whole venom (Tmax = 2 h and 1 h, respectively). Rapid absorption of the neurotoxin and cardiotoxin from the injection site into systemic circulation indicates fast onsets of action of these principal toxins that are responsible for the early systemic manifestation of envenoming. The more prominent role of the neurotoxin in *N. sumatrana* systemic envenoming is further supported by its significantly higher intramuscular bioavailability (Fmax = 81.5%) compared to that of the phospholipase A₂ (Fmax = 68.6%) or cardiotoxin (Fmax = 45.6%). The incomplete absorption of the phospholipase A₂ and cardiotoxin may infer the toxins' affinities for tissues at the injection site and their pathological roles in local tissue damages through synergistic interactions.

**Conclusion:** Our results suggest that the venom neurotoxin is absorbed very rapidly and has the highest bioavailability following intramuscular injection, supporting its role as the principal toxin in systemic envenoming.

Introduction

Snake envenomation remains a neglected tropical disease prevalent in the Southeast Asia region, including Malaysia [1,2]. It affects not only the population in the rural area but also the suburban region due to rapid urbanization, and the encroaching of human activities into the natural habitat of snakes [3-7]. In Malaysia, cobra bites appears to be one of the commonest causes of snake envenomation [4-6]. There are two species of common cobras in Malaysia: *Naja kaouthia* and *Naja sumatrana*, both classified as Category 1 medically important venomous snake [7]. Of these two *Naja* cobras, *N. sumatrana* is widely distributed in the Peninsula Malaysia (including Singapore), and is also known as the Equatorial spitting cobra [8], one of the venom-spitting species in Southeast Asia that are able to cause venom ophthalmitis. Clinically, cobra bites produce systemic envenomation syndrome with the characteristic neurovascular paralysis, and local toxicity manifested as severe tissue necrosis [2,5,9]. The characteristics of different cobra venoms, however, are necessary for the better understanding of cobra envenomation pathophysiology as the toxin composition in cobra venoms vary from species to species [10]. Recent venom profiling with the use of ion-exchange high performance liquid chromatography has shown that the major toxins of *N. sumatrana* venom comprise high abundance of phospholipase A₂ and three-finger toxins such as polyptides of neurotoxins and cardiotoxins [10]. These toxins with varied biological and physiochemical properties which make the characterization of individual toxins warranted in order to gain better insights into the toxic effects of the whole venom. The optimization of snakebite management and the use of antivenom depend greatly on the knowledge of the venom's composition, pharmacological activities, as well as its disposition in the body (i.e., pharmacokinetics). The pharmacological and pharmacological effects of snake envenomation are related to the absorption and...